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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/715,927	11/17/2000	Leonard I. Zon	1242.1035-002	6132

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/715,927	ZON ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-52,54-62,65,67,69-72,134-136,138-156* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *46,47,54-60,62,65,72 and 143-146* is/are allowed.

6)☒ Claim(s) *48,49,50,51,52,61, 67,69,70,71,134,135,136,138,139,140,141,142,147,148,149,150,151,152,153,154,155,156* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The Amendment, received 30 April 2004, has been entered into the record. Applicants cancelled Claims 1-45, 68 and 137 and added Claims 140-156. Claims 1-45 were withdrawn by the examiner in Paper 12 (31 July 2002).

Claims 46-52, 54-62, 65, 67-72, 134-136 and 138-156 are being examined in the instant Application, as pertaining to SEQ ID NO: 5, 6 and 7.

Objections/Rejections

35 USC § 112, first paragraph-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 48-52, 134 and 148-156 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nucleic acids of SEQ ID NO: 5 and 7, as well as methods of making and using said nucleotides, does not reasonably provide enablement for nucleic acids with indeterminate sequence identity to SEQ ID NO: 5 or 7 or *allelic variants or variant alleles* of SEQ ID NO: 5 or 7, or methods of detecting allelic variants of SEQ ID NO:

5 or 7, without specifying the exact sequence variation detected or the probe required. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to cDNA and genomic DNA encoding a human iron transporter polypeptide. The specification discloses human, mouse and Zebrafish iron transporters and uses the Zebrafish transporter to measure iron flux across Xenopus oocytes transfected with the polynucleotide(s) encoding the transporter. The specification also discloses methods for recombinantly expressing the disclosed transporter polypeptides. The human and mouse polypeptides have approximately 82 and 89% similarity to the Zebrafish iron transporter, respectively. Furthermore, the Applicant's post-filing-date reference demonstrates that the human Ferroportin transporter functions similarly to the Zebrafish iron transporter (Montosi, et al, 2001, J. Clin. Invest., 108(4): 619-623). However, the scope of the patent protection sought by the Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons:

The specification discloses an enabled utility for the polypeptide encoded by the DNA of SEQ ID NO: 1, as to be used to transport iron across the plasma membrane of cells expressing or transfected with the polynucleotide. Applicants have demonstrated, using transfected Xenopus oocytes, that the polypeptide encoded by SEQ ID NO: 1 (SEQ ID NO: 2) is a transmembrane transporter. Furthermore, by performing the iron flux experiments in the presence and absence of an iron chelator, they have demonstrated that the transporter binds and translocates iron exclusively and with high-affinity.

The specification discloses mouse, human and Zebrafish ferroportin transporters as well as the human transporter encoded by the DNA of SEQ ID NO: 5 and 7. However, there is no discussion, or working examples disclosed in the instant case, as to what amino acids are necessary to impart or maintain the functional characteristics of the claimed polynucleotide(s). The instant case claims altering the polynucleotide(s) encoding the polypeptide of SEQ ID NO: 6. However, as discussed in the previous Office Action (pages 6-9, 31 July 2002) the art shows that transporter families have members with high structural similarities but disparate functions. For example, Bisson, *et al* (1993, Crit Rev Biochem Mol Biol, 28:259) studied yeast transporter knockout phenotypes, and found little correlation between homology and the substrate transported. They determined that the yeast transporters *Gal2* and *Hxt4* displayed 83.7% homology, but *Gal2* appears to transport Galactose, while *Hxt4* appears to transport Glucose (based on knockout phenotype- compare Table 1 and Table 2A). Similarly, Liang et al found that several single amino acid substitutions in yeast glucose transporters can also change substrate specificity (Liang, H., et al (1998) Mol. Cell. Biol. 18(2): 926). These studies demonstrate that it is not predictable which amino acids are necessary to maintain the functional characteristics of a protein.

For similar reasons, the specification is not enabling for various regions, fragments or portions of the polypeptide encoded by SEQ ID NO: 5 and 7, as recited or encompassed by claims 48-52, 61, 134, 135, 136, 138, 139, 141, 142 and 147-156. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Claims 48-52, 61, 134, 135, 136, 138, 139, 141, 142 and 147-156 read on defined and undefined fragments of the

polynucleotide(s) encoding SEQ ID NO: 6. However, the specific activities of the proteins encoded by the claimed nucleotide fragments are not disclosed. Nor are there disclosed assays to test for these activities. There is no discussion or working examples disclosed in the instant case as to what amino acids are necessary to maintain the functional characteristics of the polypeptide fragments encoded by the claimed polynucleotides. Furthermore, the specification is not enabling for producing a fragment of ferroportin1 from the full-length sequences, as recited in Claims 155 and 156.

The specification does not reasonably provide enablement for use of the polypeptide or polynucleotide *allelic variant, variant alleles* or *allele-specific* probes, as recited or encompassed by claims 51, 134, 148, 149, 152, 153 and 154. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Applicants have not identified all allelic variants of the Ferroportin1 protein encompassed by the claims, nor of the polynucleotide(s) encoding SEQ ID NO: 6. Claims 51, 134, 148, 149, 152, 153 and 154 encompass numerous undefined variants of SEQ ID NO: 5 and 7, without precise recitations of function that apply to allelic variants, nor by reciting the precise amino acid substitutions found in an allelic variant. Furthermore, as discussed above, it is not predictable as to which possible variants are tolerated while still maintaining the functional characteristics of a protein. Applicants have submitted evidence from their laboratory indicating that the polynucleotide encoding SEQ ID NO: 6 does have a single known allelic variant, characterized by an *A77D* substitution (alanine to aspartate at residue 77) and responsible for a dominant hemochromatosis (Montosi, et al, 2001, J. Clin. Invest., 108(4): 619-623). Several other mutations and variants

have been identified previously (Donovan, et al, 2000(a), Nature, 403: 776-781; Arden, et al, 2003, Gut, 52: 1215-1217). However, claims 51, 134 and 137 read on many unidentified allelic variants, rather than the documented *A77D* substitution.

Due to the large quantity of experimentation required to: determine how to use all variants of SEQ ID NO: 5 and 7; the lack of direction or guidance in the specification regarding same - e.g., the lack of guidance regarding activity of the fragments of the polynucleotides; the lack of guidance regarding allelic variants of SEQ ID NO: 5; the lack of working examples to all possible variants of SEQ ID NO: 5 and 7; the state of the art showing the unpredictability of function based on structural similarity of transporter polypeptides; and the breadth of the claims which embrace innumerable variants of SEQ ID NO: 5 and 7-- undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

35 USC § 112, first paragraph-Written Description

Claims 51, 134, 148, 149, 152, 153 and 154 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The cited claims are directed to nucleotide allelic variant, variant alleles or allele-specific probes. The specification teaches the polynucleotides SEQ ID NO: 5 and 6. However, the specification does not teach functional or structural characteristics of all claimed polynucleotides. The description of one or two human Ferroportin 1 sequences is not adequate

written description of an entire genus of functionally equivalent polynucleotides and polypeptides.

To provide evidence of enablement of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity or protein domains that have not been adequately identified. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of all claimed polynucleotides, and therefore, would not know how to use them. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of identification or use. Adequate written

description requires more than a mere statement that it is part of the invention and reference to a potential method of use: The very nucleotide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5 or 7 and a polypeptide comprising the amino acid sequence of SEQ ID NO: 6, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 U.S.C. 112, second paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 49, 51, 52, 67, 69, 70, 71, 140, 152 and 153 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 49, 51, 52, 69, 152 and 153 are rendered indefinite because of the phrase "stringent conditions" or "highly stringent conditions" which are conditional terms. In other words, for example, some nucleic acids which are able to hybridize under stringent conditions would be unable to hybridize under non-stringent conditions. The metes and bounds of the claims, therefore, cannot be ascertained. This rejection can be overcome by supplying specific conditions supported by the specification, which the Applicants consider "stringent," or by removing the indefinite phrase.

Claims 67, 70 and 71 are rejected under 35 U.S.C. 112-second paragraph, because the claimed invention is directed to subject matter which is indefinite and may encompass naturally-occurring subject matter. The claims read on a nucleic acid which is not isolated or modified. Naturally-occurring cells can be grown in culture, and some of those cells might comprise SEQ ID NO: 6, including those from humans. Amending the claims to read an *isolated* or *recombinant* nucleic acid, etc. would be remedial.

Claim 140 is rejected under 35 USC § 112, second paragraph, for being indefinite of scope. In Claim 140 the species (SEQ ID NO: 6) follows a genus; therefore, a narrow range limitation is meant to encompass a broad range limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether

the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 140 recites the broad recitation "Ferroportin1," and the claim also recites "SEQ ID NO: 6" which is the narrower statement of the range/limitation. Amending the claim to read, for example: "a nucleotide sequence that encodes the Ferroportin 1 peptide of SEQ ID NO: 6," would be remedial.

Claim Rejections- 35 USC § 102

The following are quotations of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 135, 136, 138, 139, 141, 142 and 147 are rejected under 35 U.S.C. 102(b) as being unpatentable over Dodsworth, et al (1995, Accession No. HS153B8F). Dodsworth, et al claim a polypeptide sequence which is approximately 37% identical to SEQ ID NO: 7 and 34% identical to SEQ ID NO: 5 in the instant application. In particular Accession No. HS153B8F is identical to the reference sequences at bases 237-476 of the reference sequences. This reference

meets the limitations of Claims 135, 136, 138, 139, 141, 142 and 147 and dependent claims of a nucleic acid "15-30 nucleotides" long or of a "portion" of SEQ ID NO: 5 or 7.

Conclusion:

Claims 46,47,54-60,62,65,72 and 143-146 are allowable.

Claims 48,49,50,51,52,61, 67,69,70,71,134,135,136,138,139,140,141,142,147-156 are rejected for the reasons cited above.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW

12 September 2004

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER